

**Best Pharmaceuticals for Children Act (BPCA)
Emergency Research in Children Working Meeting
January 13–14, 2006
Bethesda, MD**

Welcome and Introduction

Donald R. Mattison, M.D., National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS)

Dr. Mattison welcomed participants to the working meeting concerning ethical, regulatory, and clinical aspects of emergency research in children. He explained that he returned to NICHD in 2002 when the Best Pharmaceuticals for Children Act (BPCA) was enacted to help build a program to implement the legislation. Because doing clinical studies on children and pregnant women raises a host of issues, he looked forward to hearing participants' expert opinions on how research in emergency settings can be conducted.

Meeting Objectives

George Giacoia, M.D., NICHD, NIH, DHHS

Dr. Giacoia explained that the purpose of the meeting was to allow a dialogue among investigators, ethicists, and local Institutional Review Boards (IRB) members to identify issues in the design and conduct of studies under emergency conditions and barriers or problems in the implementation of such studies. The subjects of these trials are pediatric neonatal, cardiac, and emergency room subpopulations. He said that this meeting was not held under the auspices of a Federal Advisory Committee Act (FACA) committee and was not intended to reach a consensus of opinions or provide advice to the government. It was not published in the *Federal Register* but was open with an invitation. Dr. Giacoia stated that federal officials at the meeting would mostly observe and provide information on policies or regulations as needed. He then asked participants to introduce themselves and describe their professional backgrounds.

After the introductions, Dr. Giacoia explained that the format of the meeting was to:

- Review the ethical and regulatory history of current emergency exception from informed consent (EFIC) regulations
- Discuss specific issues
- Gather individual participants' opinions and highlights of group discussions.

Dr. Giacoia listed the following as possible meeting outcomes:

- Publication of proceedings
- Further discussions by groups of principal investigators (for example, networks) or organizations (for example, American Academy of Pediatrics)
- Information and discussion of issues to be taken into consideration by NICHD for BPCA studies
- Determination by NICHD if a FACA compliant public meeting is needed.

Robert M. Nelson, M.D., Ph.D., Children's Hospital of Philadelphia, explained that certain processes were required because this was not a public advisory committee meeting. The goal of the meeting was to identify issues or questions, not to achieve a consensus or advise the government. His hope was that this meeting might lay the groundwork for a public meeting, but the timing of that would be affected by the release of the Food and Drug Administration (FDA) guidance on research conducted under the emergency exception. He said that a summary of the working meeting might be published in the *American Journal of Bioethics*, perhaps in association with articles on other topics related to the exception rule.

Dr. Nelson described the meeting as a "large focus group that would cover the waterfront." The agenda included a presentation on the ethical and regulatory history of waived consent followed by open discussion of five themes:

- Patient eligibility
- Study design
- Consent
- Community consultation and public disclosure
- Oversight systems.

Waived Consent for Emergency Research: Ethical and Regulatory History

Norman Fost, M.D., M.P.H., University of Wisconsin

Dr. Fost thanked the group for inviting him to reflect on the origins of the proposal to conduct research in emergency settings without subject consent. He began his presentation by saying that it had taken approximately 20 years of discussion for this type of research to be deemed ethically and legally acceptable. He added that the concept was still controversial with some ethicists, IRB members, sponsors, and the general public.

He began by discussing the following statement in Article 1 of the Nuremberg Code: "The voluntary consent of the human subject is absolutely essential." In his opinion, voluntary consent of the human subject is neither necessary nor sufficient for ethically and legally responsible research. He said that if people in Auschwitz had provided written consent for the research conducted on them, it would not justify the research. If a study was proposed to identify how close a skydiver could safely get to the ground before a parachute opened, the study would not be ethical even if the consent form clearly stated the risks. IRBs routinely reject research proposals that have poor benefit/risk ratios or are poorly designed.

Dr. Fost explained that research conducted on children and incompetent adults without their consent under certain circumstances is ethical and widely accepted. Examples are:

- Therapeutic research for which there is a reasonable prospect of benefit
- Non-therapeutic research with minimal risk.

The American Academy of Pediatrics has pointed out for years that proxy permission (for example, from parents of children) is not consent. Proxy permission provides authorization and legal protection, but it is not informed consent.

Dr. Fost said that the Declaration of Helsinki acknowledged exceptions from the Nuremberg Code for research on incompetent people under the following conditions:

- If a “responsible relative” gave permission
- If the research was consistent with national statutes
- If a physician considered it essential not to obtain informed consent and stated the specific reasons.

The DHHS regulation 45 CFR 46.116d, known as the “common rule,” allows for waiver of consent if the following four conditions are met:

- Minimal risk
- Does not affect the rights or welfare of the subject
- Impractical to get consent
- Subject is debriefed when appropriate.

He said that the first and third of these requirements make waiving consent difficult. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Therefore, the requirement for minimal risk precludes almost all therapeutic studies because they involve drugs, devices, or procedures. Proving “impracticality” is also difficult for IRBs because the “window of opportunity” is usually unknowable. Obtaining prospective consent from those at risk is possible but is expensive and time consuming. For these reasons, waivers were rarely obtained for intervention studies under the DHHS regulations.

The discussion on the concept of deferred consent began in earnest in 1980 when Drs. Fost and Robertson published a paper reporting a study at the University of Wisconsin Medical Center. Dr. Fost was at that time and still is the chair of the IRB at that medical center. In the study, an investigator wanted to compare three different doses of corticosteroids for acute closed head injury. It was standard practice at the time to use steroids to treat patients with head injuries, but different doses were routinely used, including the three doses proposed for the study. The IRB determined that this was a minimal risk study because the risk of each proposed dose was no higher than current standard therapy. In the article, Drs. Fost and Robertson called this “deferred consent,” but Dr. Fost concluded that a more proper term would have been “waived consent” for emergency research.

In 1986, Dr. Abramson and colleagues at the University of Pittsburgh published a study on the use of thiopental following cardiac arrest. They argued that this was a minimal risk study based on the differential risk between experimental treatment and standard treatment. Because many physicians already gave patients thiopental after cardiac arrest, the risk of being randomized to receive it was no higher than receiving it as part of standard treatment. Some people objected that this was giving an “experimental” or “unproven” treatment. However, thiopental was an FDA-approved drug that was widely used for this indication without any evidence. Dr. Fost found it ironic that research subjects were less likely to get the drug in the study than if not in the study. He then quoted R.W. Smithells, who asked in 1975: “Why is it that I need permission to give a drug to half of my patients but not to give it to all of my patients?”

Ernest Prentice, M.D., and colleagues published a paper in 1994 based on a study of polyethylene glycol covalently linked to superoxide dismutase (PEG-SOD) given to people with severe closed head injury at the University of Nebraska. This was justified under a minimal risk waiver because patients receiving standard care were routinely given this drug. In addition, it had few toxic effects in animal studies and in human studies for other indications. Charles McCarthy, the Director of the Office of Protection from Research Risks (OPRR) and one of the writers of the DHHS regulations, agreed that risk should be evaluated by comparing the risks of patient standard care versus the risk of being a subject in the study.

Dr. Fost then discussed the more formidable FDA regulations, which also required four conditions for waiver of consent:

- Necessary to save life of subject
- Inability to communicate with subject
- Time insufficient for legal representative
- No alternative generally recognized treatment available that provides equal or greater likelihood of saving the life of the subject.

Dr. Fost pointed out that death is not the only relevant outcome. Patients also worry about irreversible outcomes such as profound brain damage or loss of vital organs or tissues. Dr. Fost explained that the legal status of next of kin consent for research is unclear in some states and prohibited in others. The answer to the fourth criterion is unknown because until the study is done, the most effective treatment cannot be known. Perhaps most problematic, the condition requiring the necessity of saving life seemed to preclude placebo controlled trials. He said that the FDA has been the leader in mandating placebo controlled trials to give an indication to a new or existing drug. According to the FDA requirements, it is hard to argue that a placebo is required to save a person's life. However, he added that there are situations in which giving a placebo can be lifesaving. If standard treatment is toxic or ineffective, which is common in emergency and critical care settings, getting a placebo may be lifesaving. Dr. Fost quoted his colleague David DeMets, Ph.D., who said, "If I am brought to the emergency department unconscious and there is a clinical trial for my condition, I want to be in the placebo group."

Of all drugs brought to phase 1 testing, 90 percent never get to market; 50 percent of phase 3 drugs are found to be safe and effective. In general, new ideas do not work. So, being in the placebo group may be safest.

Consequences of these barriers to research created by the DHHS and FDA rules were:

- Concern that studies were being conducted outside of the rules
- Important studies were not being done
 - Inappropriately rejected by IRBs
 - Sponsors were fearful
- Fear of severe regulatory penalties
 - Shutdown of research for entire institutions (for example, Johns Hopkins)
 - "Dear Colleague" letter from Gary Ellis (Director, OPRR) and FDA officials that these interpretations of the minimal risk waiver were incorrect

- In 1994, the FDA suspended an external cardiac massage study.

Dr. Fost said that waiver-of-consent policies were changed because people who thought these regulations were not in the best interests of patients in emergency settings wrote articles, attended conferences, and spoke out. In 1994, Ron Wyden, chair of the House Subcommittee on Regulation, held hearings that were favorable to changing the rules. In 2005, Michelle Biros, M.D., and other researchers and ethicists wrote a consensus statement called “Coalition Conference of Critical Care Researchers” that was published in the *Journal of the American Medical Association*. This statement urged a change in the DHHS and FDA rules to allow research in emergency settings using a waiver of consent in certain situations. In 1995, the FDA held a conference and published a proposed rule that was finalized in 1996.

The key elements of the final rule were:

- Life threatening situation
- Available treatments were unproven or unsatisfactory
- Consent from subject or surrogate was not feasible based on the urgency of the subject’s condition
- Research could not otherwise be done
- Risks and benefits were reasonable
- Prospect of direct medical benefit to the subject.

A series of procedural protections included in the rule were:

- Consultation with the community in which the research will occur
- Public disclosure of study design and risks prior to commencement of the study
- Public disclosure of study results when completed
- Requirement for an independent Data Monitoring Committee (DMC)
- Approval of the study by FDA.

Dr. Fost pointed out that most of the studies were of existing drugs. In these cases, an investigational new drug (IND) process is not required for studying these drugs. However, in order to use the exception for research, FDA approval of the study is required. Widespread criticism resulted after the final rule was enacted. Some of the comments made were:

- “It is a fateful step...Nuremberg stands alone in its unequivocal declaration of rights...of subjects to consent.” (Jay Katz, 50th Anniversary Conference in Nuremberg)
- “Many African Americans will wonder what’s different about this [from] the Tuskegee Experiment.” (Annette Dula)
- “Most people would not want a doctor to flip a coin when they come into an emergency room.” (George Annas)
- “At least my patients gave consent.” (Jack Kevorkian).

Ethical objections to the rule included the following categories:

- Consent is an absolute principle.
- Standard for consent should be higher in research than in standard treatment.
- Patients would not want to be enrolled in a clinical trial without their consent.
- There is no justification for ever giving a placebo without consent.

In response to the belief that consent is an absolute principle, Dr. Fost said:

- Proxy “consent” is widely accepted in treatment and research settings.
- Implied consent is a familiar form of consent.
- Waived consent occurs when patients do not want to go through a consent process, including
 - Routine care
 - Research
 - Non-Western cultures (which do not highly value the principal of autonomy).
- Presumed consent
 - Particularly in emergency settings
 - Most agents would be used without consent, anyway.

Dr. Fost said that the question is not whether consent can be waived, but under what circumstances. He stressed that patients receiving the same treatment as “innovative therapy” have fewer protections than a subject in a clinical trial using waived consent. Layers of protection for subjects of studies include:

- Review of study by funding agency
- Investigators must have credentials to obtain funding
- Literature review
- Institutional review
- Careful monitoring for adverse events
- Data monitoring committees
- Studies commonly done in academic centers
- Review of manuscripts that include feedback on bad ideas.

Damages from innovative therapy in pediatrics that have occurred include:

- Sulfonamides (kernicterus)
- Chloramphenicol (“gray baby” deaths)
- Exchange transfusions done for 30 years for children with high bilirubin levels (shock, infection, death)
- Sodium bicarbonate for respiratory distress syndrome was standard practice for more than 10 years (central nervous system bleeds)
- Oxygen in uncontrolled doses (retrolental fibroplasia)
- PKU screening (mental retardation, death).

Dr. Fost described how many children were harmed by these innovative practices until research, in some cases called unethical, showed that these practices were harmful to children. He quoted Paul Lietman, M.D., Ph.D., Johns Hopkins Medical School, who said in 1971, “As long as you promise not to learn anything from what you are doing, you don’t have to go through an IRB.”

Comparisons of consent standards for research versus innovative therapy show:

- The protections are much greater for a research subject than for a patient receiving innovative therapy. For example, if the same treatment is being used, the risk of harm is greater outside of a research study (“inclusion benefit”).

- Consent should be more important in innovative therapy than in research, because other protections are absent.
- Historical reasons for insisting on consent in research settings have shifted.

Dr. Foster concluded that consent standards for innovative treatment should be much higher than those for research. A subject in a clinical trial is more likely to get rational treatment from an informed researcher than from a doctor giving innovative therapy with no protections for the patients. In fact, the risk of harm from the same agent is much higher for innovative therapy than inside a research study.

To illustrate some of these points, Dr. Foster described the first trial using a waiver of consent. The substance being studied was a semi-synthetic hemoglobin (DCLHB) used for subjects with hemorrhagic shock in the field. All subjects received standard treatment from the emergency medical team and half were randomized to receive DCLHB. The study was stopped after 10 percent enrollment but before the first meeting of the DMC due to excess mortality in the treatment group. Many assume this was due to DCLHB, but this is not clear. He asked participants to assume that DCLHB had been approved for other uses and used as innovative therapy for hemorrhagic shock. In this case, the apparent risk would not have been detected as quickly, and many more patients would have been harmed. When viewed this way, the trial could be interpreted as preventing deaths from innovative use of DCLHB.

Dr. Foster moved on to a discussion of whether it was accurate to assume that patients would not want to be research subjects without consent. He described the first empiric study of how surrogates felt about this issue done by Abramson and colleagues. The study evaluated calcium channel blockers for comatose survivors of cardiac arrest at 24 hospitals in 8 countries. The IRB required that consent be obtained before the second dose was given (8 hours after the first dose was given). Documenting the interaction with the surrogate and reporting it back to the IRB was required. Reactions to the deferred consent process were:

- 266/343 (78 percent) of surrogate's reactions in the United States were obtained.
- 120/215 (47 percent) of surrogate's reactions in Europe were obtained.
- 12 (3 percent) of families refused to continue in the study. None of the 12 reacted to the research study. All 12 objected to any medical treatment being done after a cardiac arrest.

Abramson and colleagues found that in this population, waived consent was not objectionable. Caveats were:

- Interviews were conducted after treatment was started. However, response might have been different if an attempt was made to obtain consent before treatment was started.
- Variables will be different in other trials
 - Efficacy/toxicity of standard treatment
 - Expected risks of experimental treatment
 - Cultural aspects of population
 - Trust in researchers/institution.

These are some of the reasons that community consultation is required by the regulations. Relevance of community consultation includes:

- Written surveys may not be as effective as focus groups or interviews.
 - Wisconsin Cystic Fibrosis Newborn Screening Study
 - 600,000 newborns randomized without consent
 - Focus groups: initial shock and opposition transformed to support after an hour of discussion.
- Unanimity is not essential.
- Opportunities to opt out should be provided.

Dr. Fost discussed the notion that placebos are always unjustified. He said that if a study is in equipoise, the placebo arm may be better. According to Dr. Fost, the assumption that the placebo group is disadvantaged is at the heart of the false and dangerous confidence in innovative therapy.

To summarize, Dr. Fost said:

- Informed consent is not an end in itself. It is a means to end. The end is protection from harm, and protecting the right to be treated the way a person would want to be treated.
- In emergency settings, the patient cannot be an active participant in choosing treatment; the physician must proceed on the basis of a best guess as to what the patient would want.
- If a patient would trust the physician to use unproven treatments as innovative therapy, then such trust could be presumed to extend to using the same treatment as part of a well reviewed, well designed, controlled, and monitored study.
- Using untested therapies outside of a well designed trial is more likely to result in harm, often without compensating benefit, and with no way of knowing whether patients were harmed or helped. This is an outcome most patients would presumably not want.
- Rules that foster innovative therapy and inhibit research are bad social policy. They result in substantial harm and little progress in scientific knowledge. This is not the strongest argument for waived consent; it is the interests of the individual patient that provide the strongest justification. Societal benefit is an added benefit.

In conclusion, the goal of the revised rules was to correct several problems, resulting in:

- Improvement in the rate of progress in emergency care, for the benefit of future patients
- Improvement of the likelihood that patients will be protected from harmful or ineffective treatments
- Increased likelihood that patients will be managed in the way they would want to be, if they were fully informed.

Discussion of Process and Overview

Dr. Fost opened the discussion for comments or questions. Leonard Glantz, J.D., Boston University School of Public Health, said that Dr. Fost made an excellent argument against off-label use of medications by physicians. However, he described some problems with the analysis that Dr. Fost presented. He asked for more careful use of the terms “researcher,” “physician,” “patient,” and “subject.” The role of a physician is to benefit the patient; the role of a researcher is to obtain knowledge. Loyalties and trust in research/subject relationships are different than those in doctor/patient relationships.

Mr. Glantz disagreed that the Nuremberg code was wrong. In the context of the Nuremberg code, where it was obvious that research that might benefit subjects was not occurring and where the risk was high, informed consent is absolutely essential. He said a good argument could be made for the proposition that any research that puts human subjects at risk without potential benefit requires informed consent. He added that the discussion should start with the proposition that research without informed consent is unethical. Research without consent for very particular circumstances requires powerful justifications and great care. He then paraphrased Hans Jonas who said scientific progress is an important goal but an optional good, whereas respect for human beings is a mandatory good. He acknowledged that Dr. Fost made a powerful argument for this type of research, but equally powerful ethical arguments that go beyond risk and benefits need to be made during this meeting.

Dr. Fost replied to Mr. Glantz's argument by saying the distinction between good medical care and good research is not so clear cut. He said that good medical care requires providing treatment that is based on data, not opinions. As a doctor, it is more responsible to patients to use agents in research settings. Mr. Glantz responded that researchers are bound by the protocol, not necessarily what they think is in the subject's best interest. Dr. Fost said that physicians who think a trial is not in a patient's best interest should not invite that person to participate in the research. Mr. Glantz pointed out that one cannot have it both ways.

Neil N. Finer, M.D., University of California, San Diego Medical Center, said that benefits of research include benefits not just for the individual enrolled in the trial, but also benefits for future patients based on results of the research. The central question for each study should be in equipoise because the best treatment is not known. DMCs and IRBs determine that there is not excessive risk when they approve studies and thus there is significant protection for subjects. This is not true with innovative therapies. He concluded that physicians do not give up the best interests of patients when they suggest a clinical trial.

In response, Ernest Prentice, Ph.D., University of Nebraska Medical Center, described the Phillips case in Philadelphia in 1999. A patient had a large arteriovenous malformation in his brain that was too large for surgery. He was given innovative therapy of hyperfractionated stereotactic radiation therapy. After Mr. Phillips went into a coma, his wife sued. During discovery, it was determined that the innovative therapy was identical to a proposed study that had not yet been submitted to the IRB. However, the neurosurgeon had used the draft consent form with the family. The legal issue became whether this was innovative therapy or experimentation. The outcome was a \$10 million+ settlement with the family before the case went to trial. Dr. Prentice said that one should not deviate from standard practice unless a protocol has been approved by the IRB.

Stanley J. Szeffler, M.D., National Jewish Medical and Research Center, asked Dr. Fost how rationales are developed for new research. Dr. Fost said that each case is different. He pointed out that 80 percent of pediatric prescriptions are for drugs used off label. The ideal situation would be that the first patient who receives a new treatment should always be randomized, but that is not going to happen.

Dr. Nelson summarized the discussion by saying:

- If a doctor is giving drugs in the absence of evidence, it is doubtful if he or she is acting in the patient's best interest.
- The distinction between clinician and researcher in terms of the protocol becomes problematic if it is not known which treatment is in the patient's best interest.

Jon E. Tyson, M.D., M.P.H., University of Texas Medical School at Houston, suggested not discussing physicians' and researchers' motivations. He said that anyone who goes to the trouble of going through what is necessary to plan and run a clinical trial cares about patients. He said that the question should be, "What is the evidence that a subject in a trial is worse off than a patient getting innovative therapy?" He concluded that people receiving innovative therapy require more protection than do those enrolled in trials.

Glenn McGee, Ph.D., Alden March Bioethics Institute, described the concept of therapeutic misconception, which occurs when physicians without adequate knowledge offer innovative therapy to patients. When a researcher suggests a trial to a potential subject, he or she ceases to be able to fulfill all of the unique aspects of the role of a physician. Dr. Fost reviewed the conflicts and mixed motives for researchers, who may:

- Want to advance knowledge
- Get famous
- Obtain grants
- Go on a lecture tour.

Dr. Fost said it would be helpful to ask what an unconflicted advocate would recommend. He believes that the answer would be a randomized clinical trial, and he pointed out that this is the reason for requiring community consultation.

Ken Kipnis, Ph.D., University of Hawaii at Manoa, asked whether Dr. Fost was recommending:

- Waived consent trials when equipoise is necessary between interventions that are both unproven but in widespread use as innovative therapies
- Extension of applicability beyond situations involving the possibility of death to those with possibility of permanent loss of function.

After some discussion, Dr. Fost said yes to both questions. Benjamin S. Wilfond, M.D., National Human Genome Research Institute, NIH, DHHS, asked about collection and use of data in clinical studies. He wondered what is done with samples and data when subjects enrolled without consent withdraw when asked for deferred consent. Dr. Fost said that mortality data cannot be withdrawn; however, in general, most data can be withdrawn.

Alan R. Fleischman, M.D., NICHD, NIH, DHHS, suggested asking if randomized clinical trials are always the gold standard for drugs currently in use. Nathan Kuppermann, M.D., M.P.H., University of California, Davis Medical Center, said that in Britain a randomized clinical trial cannot be done unless a meta-analysis has been completed and shows true equipoise. He wondered if this should be required in the United States as well.

Discussion of Issue #1: Patient Eligibility

What conditions qualify as “life threatening”? On what grounds can existing treatment be considered “unsatisfactory”?

Dr. Nelson reviewed the five themes for discussion, acknowledging that areas of discussion may overlap:

- Patient eligibility
- Study design
- Consent
- Community consultation and public disclosure
- Oversight systems.

He said that the intent is not to discuss specific trials, but that concrete examples may help the theoretical discussions produce practical suggestions.

Dr. Fost began the discussion by saying that after 20 years’ effort to change regulations to allow this type of research, barriers still exist. He suggested separating ethical from tactical arguments and focusing on randomized trials that deal with life threatening issues. Although Mr. Glantz appreciated the distinction, he noted that the FDA required life threatening situations because of the underlying ethical issue of performing research without consent. So it is an issue of ethical justification as well as tactics.

John D. Lantos, M.D., University of Chicago, suggested expanding “life threatening” to include situations in which an intervention must occur immediately in order to avoid serious health consequences, such as a child having a seizure. Dr. Nelson said that life threatening could be interpreted as a condition that, if left untreated, could possibly lead to a threat to life. Using this definition, an infection that might develop in the future in a person who was immobile could be considered potentially life threatening. It was pointed out that most IRBs would not interpret life threatening that way. Several participants thought that the definition could be stretched to include “permanent loss of function,” although they thought that tactically it might make sense to set that notion aside.

Mr. Glantz said that the FDA preamble suggests an expanded definition of life threatening, but the rule does not support that interpretation. He also clarified that the rules do not say life threatening condition, but do say “life threatening situation” that “necessitates intervention.” A discussion ensued and several portions of the preamble and the rules were read aloud. Regardless of the intent of the people who wrote the preamble, Mr. Glantz said that the rules requiring a life threatening situation must be followed.

Dr. Fost said that in modern emergency rooms and intensive care units, life can be prolonged for great lengths of time. He thought many patients are more frightened of brain death or loss of limb than death. He suggested using “severe irreversible harm” as the definition under which research could be done without consent. Janice E. Sullivan, M.D., University of Louisville,

encouraged including quality of life in the definition, using children who suffered multiple seizures as an example.

Dr. Wilfond asked participants to clarify what was delaying research using the new regulations. His reading of the background materials suggested that it was the restrictive nature of the regulations that erected barriers to research, but discussions during the meeting suggested that sponsors and IRBs were hesitant to approve or conduct research without consent despite the new regulations. Paula Knudson, University of Texas, Houston, mentioned the timidity of some IRBs to use the exception to informed consent. Dr. Kuppermann said that some would argue that the regulations have improved research. He also suggested more careful use of the terms “exception” and “waiver.”

Dr. Tyson’s view was that there are too few studies of life threatening conditions of neonates. He remarked that of 24 therapies commonly used in the first hour of life, only 2 had been evaluated. Two reasons for this are that it is often difficult to obtain IRB permission for studies and that obtaining consent is often impractical. He used cord clamping as an example. Several participants considered the economics of obtaining consent to be a red herring, while others explained why having people available 24/7 to consent families was a true barrier to research at their institutions.

Dr. Lantos said that the current regulations, while better than they used to be, still foster innovative therapies and discourage research. He pointed out that most IRB chairs have not studied research regulations in children and do not have a professional interest in encouraging such research. He said obtaining IRB permission to do research that involved children, waivers, or emergency settings is difficult. Research that involves all three is often avoided by requiring investigators who bring a proposal to these IRBs to resubmit or to contact the department of legal affairs.

Mr. Glantz cautioned participants from broadly interpreting terms in the regulations. He added that the reason some of this research is not done is because it is ethically questionable. He also suggested distinguishing between research with non-consenting subjects when there is surrogate consent and research with non-consenting subjects when there is not surrogate consent.

Walton O. Schalick III, M.D., Ph.D., Washington University in St. Louis, remarked on 60 years of shifting definitions within different historical contexts. He feels that the regulations are catching up with social needs and perceptions that quality of life requires inclusion. Mr. Glantz again said that discussion about changing the regulations to include more broad definitions was fine, but interpreting the present regulations more broadly was wrong.

Dr. Szeffler pointed out that some research focuses on developing better therapies while other studies try to better understand the science underlying illnesses such as asthma. He added that he preferred the term “serious irreversible damage.”

Dr. Nelson summarized the discussion on eligibility as follows:

- The regulations clearly say “life threatening.”

- The preamble suggests more broad interpretation.
- It is likely that an IRB will interpret the term narrowly.
- The draft guidance does not include language from the preamble.

Mr. Glantz said that the preamble is not part of the regulation, so interpretation cannot be based on it. Changing regulations requires a broad public process that provides much legitimacy. Dr. Nelson mentioned the public process used to develop the FDA guidance document that will soon be released. Dr. Prentice cautioned participants on overly broad interpretations of either the preamble or the regulations. The preamble is fairly restrictive in terms of life threatening situations. He doubts that it would include loss of a limb. Deviation from the preamble requires either a revision of the regulations or publishing a notice in the *Federal Register*.

James Chamberlain, M.D., Children's National Medical Center, discussed the concept of "proven therapy" using cardiac arrest in children, which only 5 percent survive, as an example. If epinephrine increased the survival rate to 6 percent, would that be considered a proven therapy? If animal studies of another agent suggest a survival rate of 10 percent, should that agent be studied in the context of this regulation? Dr. Kipnis described three hypothetical scenarios in which approved drugs increase survival rates from 5 to 10 to 90 percent. Are all three drugs considered unsatisfactory? He believes consent cannot be waived if substantial evidence exists that an approved treatment modality offers significant increased survival over no treatment at all. But guidance on how to make these distinctions would be very helpful.

Jill M. Baren, M.D., Children's Hospital of Philadelphia, said that scientific judgments might be based on percent increases in survival, but societal judgments are based on acceptable levels of mortality and morbidity. Then there are individual judgments that may further lower the threshold for what is considered satisfactory or unsatisfactory. Dr. Wilfond added that study design is a factor as well. One therapy might be compared to a placebo while another might be compared to an existing therapy that might improve outcome.

Dr. Kipnis said that if an unproven and unsatisfactory treatment can be reasonably withheld by a clinician, then the standard is met. If, however, a clinician would not withhold the intervention, then waived consent trials should be ruled out under the existing rules. Dr. Tyson said that "widely used" should not be considered "proven." Instead, it should be based on evidence of benefit. Dr. Fost reiterated the long history of treatments used for years (for example, sodium bicarbonate) with no evidence of benefit that were later proved to be harmful. Dr. Lantos said the concept of equipoise works better than does the term "unsatisfactory." Dr. Fost noted that the FDA guidance does allow for withholding treatment (page 5 of the 2000 guidance) to determine if the standard treatment is useful.

The discussion returned to unproven, and sometimes harmful, treatments that are contained in professional treatment guidelines. Arthur R. Derse, M.D., J.D., Medical College of Wisconsin, described a study done in the 1980s at the Medical College of Wisconsin to determine whether or not calcium chloride was effective in treating cardiac arrest. At that time, the advanced cardiac life support (ACLS) guidelines mandated using calcium chloride as part of treatment in this situation. In the study, calcium was compared to a placebo. The study showed that calcium

chloride actually killed people. At the time the study began, calcium chloride was standard treatment for cardiac arrest, but after the study results were evaluated, it was no longer used.

Dr. Finer said that he would like to use the emergency exception to provide treatments that have the potential for improving outcomes, if current therapies provide only minimal or uncertain benefit. Dr. Nelson suggested that the exception may only be justified when there is no equipoise in either direction. Jerry J. Zimmerman, M.D., Ph.D., University of Washington, mentioned that there may be evidence of efficacy in adults but none for treatments for children. Dr. Lantos said that in any clinical situation, something is always done, because doctors believe that the treatment will be more helpful than harmful. One cannot decide something new is better until it is tested. If one is uncertain which treatment would be better, then there is equipoise and a randomized clinical trial is acceptable. If consent is impossible, then an exception would be appropriate.

Benjamin Friedman developed the concept of equipoise, and he understood it as a characteristic of the profession as a whole, not of an individual clinician. So, if the profession does not have an evidence base that settles the matter, it is equipoise. Dr. Kipnis understands the regulations to say that with equipoise the research can be done, but not with the emergency exception. The exception requires that the only treatments available are unproven or unsatisfactory, and that is a different criterion than equipoise. Dr. Derse stressed the importance of defining unsatisfactory prior to community consultation. The original thrust for the exception was based on situations with dismal outcomes. The group discussed at some length the reasons for preferring use of the equipoise concept rather than the term satisfactory.

Dr. Nelson provided an example to help frame the discussion. He asked whether a trial using the emergency exception could be done to evaluate the efficacy of diazepam compared to lorazepam. Diazepam is labeled by the FDA for treating seizures. Using the equipoise definition, it would fit. Using the satisfactory definition, one would have to argue that the drug labeled by the FDA is unsatisfactory for the intended use.

Dr. Fost said that equipoise is not necessary for an ethically acceptable trial. He provided three examples:

- Short course AZT trials in Africa (not in equipoise)
- Sodium bicarbonate study (Drs. O'Donnell and Simmons thought sodium bicarbonate was harmful; the neonatal community said it was not in equipoise and that the study was immoral)
- Calcium chloride study for cardiac arrest (no equipoise—the community of emergency physicians mandated its use in their guidelines).

Dr. Tyson said that equipoise needs to be evidence based. There was no evidence that sodium bicarbonate was effective. If the equipoise language is used, it should be accompanied by a review of available data. Dr. Fost was asked what criteria he uses, if not equipoise, to determine if a trial is ethical. He answered that he used traditional criteria including good design, local institution review, good benefit/risk ratios, and community wishes and needs.

Dr. Kuppermann raised the issue of time to obtain consent, using bronchiolitis as an example. There is usually not time to go through a long-form consent process, but a short form probably can be used to obtain consent during the short window of opportunity. He added that equipoise would also require a suggestion of benefit. As an example, a colleague did a Cochran report on the benefits of steroids for people with closed head injuries, which showed a possible tiny benefit but also suggested harm. He added that in the last few years, it was established that putting babies to sleep on their backs lowered the incidence of SIDS. If that had been known 2 decades ago, thousands of babies' lives would have been saved. He also suggested including in the discussion the trials that evaluate diagnostic testing.

Dr. Chamberlain returned to the example posed by Dr. Nelson on comparing diazepam and lorazepam. In community hospitals around Washington, DC, 20 percent of children who get diazepam need to be intubated due to respiratory depression. Therefore, he would argue that diazepam is not satisfactory, because lorazepam probably has a better safety profile and lower rates of intubation.

Dr. Prentice reminded participants that the discussion concerns life threatening situations in which the standard treatment is unproven or unsatisfactory. If standard therapy is unproven but widely used and it is considered satisfactory, then equipoise should exist before a randomized clinical trial is used to evaluate a new treatment. On the other hand, if standard treatment is unsatisfactory, then equipoise is not necessary in order to offer an experimental treatment that offers a greater prospect of benefit.

Dr. Fleischman suggested that the definition of "unproven" should be that the evidence does not support the indication. FDA approval does not mean that the treatment is satisfactory, but only that it is indicated (has some proven efficacy within a reasonable toxicity range). Unsatisfactory is based on the level of effectiveness and the level of toxicity. Dr. Tyson said that unproven is automatically unsatisfactory.

Dr. Sullivan expressed concern that bias is introduced into studies when clinicians pick and choose who to enroll in the study. For example, some physicians will not suggest to very ill patients that they consider a clinical trial. If studies are conducted without consent, will there be sufficient buy-in from the staff so that bias will not be introduced? Mr. Glantz described a situation in emphysema studies in which a group of physicians said they knew who would benefit from the study and only recommended those patients. The sponsor told them that they would be excluded from the study because decisions for all patients need to be based on the protocol. This is an example of the difference between being a physician and a researcher.

Dr. Nelson summarized the discussion:

- Available treatments are either unproven (based on evidence), satisfactory (based on evidence), or unsatisfactory.
- An absolute interpretation of equipoise (how bad does the existing treatment have to be?)
- A relative definition of equipoise (how does it compare to something else?)
- FDA approval does not mean that the treatment is satisfactory.

PolyHeme (artificial blood) was raised as an example by Mr. Glantz. A study was proposed to give patients in hemorrhagic shock PolyHeme instead of blood. The manufacturer's argument was that blood is unsatisfactory because some people who get it develop multiple organ failure. The IRB at Mr. Glantz's institution laughed at the idea that blood was an unsatisfactory way to treat people in shock. They recognized that something might be found to be better, but they were not prepared to withhold the blood because the PolyHeme might perhaps prevent some side effects from happening later. A discussion ensued on the possible benefit of the alternative treatment.

Discussion of Issue #2: Study Design

What experimental treatments provide a sufficient "prospect of direct benefit" in the context of "unsatisfactory" treatments? What evidence is needed to establish this prospect?

Dr. Nelson said that the previous discussion focused on patient eligibility and the next segment would focus on study design, including the language in the regulations on the prospect of direct benefit. He was interested in the relationship between a trial that would fit the emergency exception and Subpart D. He thought that the concept of incremental risk versus the emergency waiver was worth discussing.

Dr. Prentice said that if a standard treatment is deemed unsatisfactory and the experimental treatment appears to offer a better prospect of direct benefit, there would be no requirement for equipoise and it would provide more justification for an exception to consent. Classification of pediatric research involving exception to informed consent would have to be under 45 CFR 46.405, which requires a relationship between the risks and benefits of research and available alternative approaches.

Dr. Kipnis said that he was struck by the exclusions. The PolyHeme study compared PolyHeme to saline as a placebo; the first phase of the study occurred during transport by ambulance. The protocol design excluded children under the age of 18 and pregnant women. Dr. Prentice said that from a regulatory viewpoint, the research is not minimal risk, so one must evaluate the prospect of direct subject benefit. If there is a direct benefit, it could be classified under 45 CFR 46.405, which requires looking at available alternatives. If there is no direct benefit, one could look at 45 CFR 46.406, which requires only a minor increase over minimal risk. The corollary FDA regulations are 21 CFR 50.52 and 50.53. In his opinion, the PolyHeme trial would not qualify, and one would have to refer the protocol to the DHHS committee. Dr. Nelson said that children would normally only get saline for hemorrhagic shock in an ambulance, so there are no alternative therapies, and therefore children would not have to be excluded from the trial. Dr. Nelson said that the regulations require a direct benefit, which is more than a balance between the two arms.

Dr. Fleischman explained that historically, adult clinical trials with risky interventions were always done before trials with children, although many child advocates argue that this is an unfair approach. Mr. Glantz said that the regulations are designed to allow research interventions to save lives. In terms of research design, this type of research should not be done if the

information can be obtained from a consenting population. For example, he asked if the PolyHeme question could have been answered by consenting adults undergoing cardiac surgery. Dr. Nelson said that during product development, an in-hospital study had been done. Dr. Kipnis clarified that just as he would favor using adults over children in initial trials, he would want to favor consenting adults over those who cannot consent. For instance, rather than testing PolyHeme on adults or children in ambulances, why not test it on Jehovah's Witnesses who would refuse blood products as a treatment option?

Dr. Lantos discussed the recurring problem of saying that studies can only be done if it is known that direct benefit will result versus doing trials because the answer about whether the treatment is better than the standard is truly not known.

Dr. Fost said that the FDA and NIH required including children in all studies unless there are specific reasons to exclude them. Dr. Nelson said that the FDA defines adults as 16 and older, so Subpart D would apply. He also raised a question about whether in a study comparing two treatments (for example, lorazepam versus diazepam) the experimental agent needs to address what is considered unsatisfactory about the current treatment. If apnea is the main concern, does lorazepam have to be equally effective in treating seizures but also have less effect on breathing in order to obtain an exception from informed consent? A participant said that an argument could be made that this trial would qualify for a waiver of consent because of the minimal risk. The adult literature (meta-analysis and a Cochrane review) both show equal effectiveness and a lower risk profile for lorazepam. Dr. Derse said that the Cochrane study, which grouped studies that on their own did not have sufficient power for definitive evidence, suggested a better safety profile for lorazepam.

Dr. Finer said that usually long-term gain or loss is not known, especially for neonates. This is especially a problem with Cochrane analyses. Incremental risk includes knowing about longer term outcomes, such as cognitive problems several years later. He characterized this issue as a major problem when using meta-analyses. In neonates, many times drugs that were effective short term were discovered to cause long-term problems. Dr. Finer pointed out that use of a drug for decades for a certain indication provides no consolation about lack of long-term effects, for instance, using phenobarbital for seizures. He said that longer term benefits and risks need to be included in study design.

The uniqueness of lorazepam and diazepam was mentioned by Dr. Fleischman. Dr. Chamberlain said a case control study from Syracuse was done when lorazepam was first introduced. When the two groups were compared, lorazepam was associated with fewer respiratory side effects. Most practitioners now use lorazepam. Dr. Tyson said that even if cohort studies look convincing, they are not sufficient. Recent experience with postmenopausal use of hormones is a good example of how animal and cohort studies suggested that they improved cardiovascular outcomes. He did not see why case control and cohort studies are necessary before randomized trials, especially for drugs currently being used. Dr. Fleischman said that for trials using exceptions from obtaining consent, these prior studies might not be sufficient but may be necessary.

Dr. Nelson described a hypothetical clinical trial with three arms including two interventions and a comparator. He said to assume that labeling is irrelevant, but there is sufficient evidence base to show that both interventions are more effective than a placebo; however, no head-to-head comparison has occurred. Assume that informed consent is not feasible. Given that both drugs are given across the country by well-meaning physicians, would the risk of the research be the incremental risk of getting them in practice? Could consent be waived because it is minimal risk, or would one have to pursue an exception? Dr. Fleischman said that consent is not just symbolic, especially when it is foregone for either a waiver or an exception. He said if both drugs were given routinely around the country, then either a waiver or an exception could be justified. Mr. Glantz pointed out there is no FDA waiver of consent in minimal risk situations.

Dr. Prentice reviewed the language that defines minimal risk, which stated that the risk would be equivalent to a well child visit to a pediatrician. Dr. Nelson said that the Institute of Medicine (IOM) interpreted it as an equivalence of risk. Mr. Glantz said the regulatory concern is that the study outlined by Dr. Nelson could be published in the literature but could not be submitted for labeling purposes.

It was noted that in the Pediatric Emergency Care Network (PECARN), approximately 20 percent of centers use diazepam. Participants wanted to discuss incremental risk using lorazepam and diazepam as an example because it is a very important issue. If outside of a study children could be given either drug, and each has a risk of causing respiratory depression, the incremental risk is the risk of being in the study compared to the risk if not in the study. In this situation, the risk is quite minimal. Dr. Nelson noted that Subpart A (section 111) requires that IRBs consider the risks of the research.

Marilyn Morris, M.D., Columbia University, recommended including the perceived risk of the research based on her conversations with parents. Most parents feel that the child's doctor is better able to decide what is best for their child than a research study is. Therefore, they think participating in a study is risky. Dr. Fost said that the IRB should make an objective analysis of the risk, but the public relations issue is a separate problem. Returning to the incremental risk issue, he said if the child goes to a center that gives the drug thought to be riskier, then the risk is not minimal. Incremental risk only applies if the subject is equally likely to get either drug.

Dr. Giacoia said that an ongoing conversation has occurred with FDA about starting this study. One of their suggestions was to have the PECARN centers alternate the use of the two drugs as part of their standard of practice. Dr. Giacoia did not think this would be acceptable to IRBs. Dr. Fost said that some institutions and networks were avoiding IRB oversight by comparing drug A to drug B as a quality improvement endeavor. Dr. Tyson described another gray area between experimentation and clinical care called the "play the winner" rule. To assess short term outcomes, institutions may use treatment A until there is a failure, then treatment B until there is a failure.

Dr. Wilfond described two definitions of minimal risk that emerged during the conversation:

- No definitive evidence that either arm is inferior
- No suggestion in the available data that either is inferior.

Mr. Glantz said that neither has to do with the regulatory definition. Dr. Fleischman pointed out that one does not need minimal risk for the emergency exception. A regulatory discussion ensued about the language in various regulations that defined minimal risk and how it can be applied to the situations previously described. Mr. Glantz said that determining how to apply specific regulatory language requires a room full of lawyers. The language in 45 CFR 46.406 applies to research that is commensurate with what would be expected in medical care (that is, “sick kids”). “Minimal risk” regulatory language uses normal healthy children as a point of comparison. For him, it is better to focus on the most appropriate way to manage these issues and to whom they apply. According to Dr. Fleischman, the central question is, “Is the incremental risk of the research equivalent to that of normal healthy children living in safe environments?”

Dr. Fost gave an example to clarify risk. He asked the group to consider entering a child having brain surgery into a study of EEG changes during brain surgery. The patient is already on a brain monitor, so the study would only get a copy of the EEG. This is a zero risk study, even though the child is having brain surgery (a very risky procedure). Consent forms for the EEG study would not mention the risks of surgery. Similarly, if two anticoagulants are routinely given at hospitals (each given to 50 percent of the patients), a study that randomizes a subject to receive one or the other is a zero risk study, even though the drugs are risky. The regulations and ethics refer to any additional risk resulting from being a research subject.

Another participant mentioned one expedited review category specifying an agent not under an IND and with minimal risk. He suggested the group look at that category for FDA approved agents. Dr. Szeffler said that incremental risk was not a helpful term in the context of a randomized control trial. He preferred the term relative risk which can show superiority or equivalence of the arms. Dr. Tyson reminded participants that trials can reduce risk to subjects, for example if the trial specifies diagnostic tests (for example, MRI) or experienced personnel to perform procedures (for example, intubation). A randomized trial being considered in the network to expose resuscitated babies to different concentrations of oxygen might reduce risk of death from a decades-old practice of giving babies 100 percent oxygen.

Dr. Morris said that even if minimal risk trials obtain IRB approval, parents may not perceive the risk to their children as minimal. Using the exception route provides additional layers of protection and may be more acceptable to parents. Dr. Nelson said that morally he understood the point, but empirically the data show that only about 5 percent of parents even understood that a trial was going on.

Dr. Nelson summarized the discussion on study design as follows:

- Ways to broaden the definition of “life threatening” either through guidance or regulatory change.
- “Proven” is based on literature and data, not just labeling.
- “Unsatisfactory” may be a more flexible standard because it allows for comparison of interventions, even if both are thought to be both safe and effective.
- Prospect of direct benefit, including Subpart D.
- Difficulty of defining minimal risk, even if incremental.

Other participants added the following summary points:

- It is easier to justify exception waivers than minimal risk trials to parents.
- Criteria for minimal risk include:
 - Both intervention strategies fall within standard practice (coin toss)
 - No definitive evidence that either is inferior.
- Even if using minimal risk criteria, it is still politically and socially a good idea to do community consultation.
- Base policies on protecting subjects rather than preventing lawsuits.

Discussion of Issue #3: Parental Permission

In pediatric research, when can we consider informed parental permission “not feasible”? How does the presence of the parent (or legal guardian) impact on feasibility?

Dr. Nelson opened the session by listing possible topics for discussion: meaning of feasibility, parental presence, and therapeutic window. Dr. Finer then introduced a number of issues related to resuscitation research on newborns:

- Mother may need urgent treatment that does not allow permission discussions.
- There may be lack of maternal clarity due to illness or medication.
- Child may have only one parent.
- Researchers do not want to exclude the most-at-risk infants.
- If at-risk infants are excluded, results may not be reproducible or generalizable.

The practice at Dr. Finer’s institution has been to use the waiver and then inform the family after the delivery to obtain permission to continue the research and use the data collected. An example of this type of research was to compare the use of continuous positive airway pressure as a form of respiratory support in the delivery room versus no respiratory pressure. Both treatments are in current practice at many institutions. The researchers have used a blended approach based on established rules for when to obtain permission. If the mother is in the hospital for an hour or two prior to childbirth and is able to talk with researchers, they obtain permission, even though they have the IRB’s permission to waive consent (minimal risk). If they use the waiver, they talk with the parents as soon as they are able to communicate.

Dr. Nelson remarked on the bias introduced when certain infants are excluded when it is not possible to obtain permission. This raises two issues regarding feasibility:

- Ability to get permission from the individual
- Ability to get permission from the entire population.

Dr. Fost asked Dr. Finer if studies could be done sequentially. First, test only the babies for whom permission can be obtained. If arm A is better than arm B, then extend the study to the sickest babies for whom permission is harder to obtain. Dr. Finer said it was possible, but the numbers of babies to test are small. He explained that out of 100 babies, only 20 might need positive pressure, 5 might need intubation, and 1 might need CPR. If the researchers are testing an intervention that is needed only by a small number of these babies and if most of them are

born to mothers who are acutely ill, then the study will take an inordinately long time to complete. Dr. Finer also discussed the problem of consenting four mothers for every one baby enrolled in a trial, exposing the mothers to unnecessary stress.

Dr. Kipnis described two concepts of community: geographic and population of susceptible individuals. For a study of miscarriages, the population of susceptible individuals is reachable through obstetricians. Two possibilities are:

- Obtaining prospective consent
- Doing community education.

The concept of a two-stage consent involving a short form used prior to delivery and a longer form with more detailed information after delivery was discussed. This led to an exchange on the amount of time necessary to obtain a meaningful consent.

Dr. Baren shared some of the challenges of conducting research in an emergency room setting. She is the site principal investigator for a pharmacokinetic (PK) study on the effectiveness of lorazepam on status epilepticus. Because the FDA did not originally allow the emergency exception for this trial, 10 different sites used a preconsent process. They screened more than 1,100 patients prior to the event occurring and re-consented upon presentation. Of the parents of the 500 children eligible, 97 agreed to preconsent, and 4 children were actually enrolled. Another feasibility issue for this trial concerned a different cohort (individuals who were evaluated in the emergency room). Out of 31 evaluated, none met the criteria for the PK trial. The researchers also conducted focus groups with investigators and research coordinators about the emotional difficulties of consenting parents during a narrow therapeutic window in a chaotic environment. The investigators were uncomfortable and they explained that discussion with parents under these conditions did not result in an effective and appropriate parental permission discussion.

Dr. Szeffler mentioned other issues:

- The stress on the investigators when obtaining consents in the emergency room
- Staff availability to obtain consents
- Finding a quiet place in the emergency room that allows a private discussion
- Investigator has no prior relationship with the family
- Ethical problems if the investigator is the treating physician.

Dr. Nelson said that he did not think that staff availability could ethically justify use of an exception for consent. Dr. Fleischman remarked on how impressive Dr. Baren's points were and said that he hoped she would publish them so others could benefit from that information. He said that the emergency waiver was designed to address these types of situations when there are only moments available to begin research. He is less sympathetic to the situation for neonates and thought that the sequential approach discussed earlier might work well.

Dr. Fost said that when an identifiable group exists (children who have seizures and may appear in emergency rooms in status epilepticus), efforts could be made to solicit them through support groups, Web sites, neurologists' offices, and the like. This allows a lengthy time for education and consent. Dr. Chamberlain contrasted this approach by describing a study in California that

showed more than half of parents whose children were having febrile seizures thought the child was dying. This is not a “teachable moment.” Mr. Glantz said that parents of very sick children are an extremely vulnerable population. He made two additional points:

- Do not use the term “preconsent.” The regulations allow consent to occur at any time.
- If staff is not available to consent people late at night, simply do not enroll people then.

Dr. Tyson made the following points about cord clamping:

- When the cord is clamped may determine whether babies die or are handicapped.
- It is disrespectful to a mother to give her a badly handicapped child if the handicap can be prevented.
- Consent is a charade if given by someone (for example, a resident) who is not knowledgeable about the trial.
- Available resources do affect whether or not a trial is financially and scientifically feasible.

The emergency exception refers to the feasibility of getting consent. Even in the waiver for minimal risk research, most IRBs apply it based on the feasibility of getting consent. So, from an ethics perspective, Dr. Nelson said that feasibility is based on the subject’s availability, not real-world staffing issues. Dr. Wilfond said the issue of adequate staffing revolves around how funding agencies want to spend their research dollars.

Dr. Lantos wondered whether it would be acceptable or unacceptable to do community consultation, without getting consent, with a community of pregnant women. He suggested asking women if they would prefer to have the study explained to them while they are in labor or be enrolled with no consent and discuss it later. Dr. Nelson said that there is literature on asking the community about feasibility. Dr. Morris said that she had spoken to focus groups and had spoken one-on-one with parents of children in pediatric intensive care units about this issue. She thinks that getting a preconsent from parents whose children may be in a particular situation in the future is not meaningful. When a child is in a particular situation (for example, cardiac arrest), parents’ feelings and responses are frequently quite different. She asked parents if they could give a meaningful consent in the 2 hours after their child was resuscitated, and they almost unanimously said no. However, the parents said they would like to receive handouts when their child entered the hospital so that they would know in advance what research studies are being done. Some parents wanted to be able to opt out in advance. Dr. Morris developed handouts, gave them to parents of 91 children, and asked:

- Did you read it?
- Did you understand it?
- Would you let your child participate if asked?

She discovered that randomized studies of two existing therapies were most acceptable to parents. After reading the handout and with several caveats, 89 percent of parents said they would let their child participate.

Dr. Prentice asked what a “reasonable person’s standard” was. In a focus group of a valid population, what percent need to approve waiving consent for that trial? Dr. Nelson said this brings up the issue of how to assess community consultation, which would be discussed later.

At the 2004 IOM meeting on clinical research in children, a lawyer father of a child who had died on a cancer clinical trial presented. In preparation, he looked at the clinical trial consent that he had signed, and he was certain he had never seen it before. However, he said there was something symbolic and respectful about the process, even though he could not make an informed consent at the time. IRBs can waive parts of informed consent, allowing the process to be respectful and not abusive. Dr. Lantos remarked on how robust the ideas of how consent should be obtained are against the overwhelming body of evidence telling how parents actually experience it. Their experience bears no resemblance to the moral ideals or legal rights consent is supposed to protect and enshrine.

Dr. Morris responded that parents want maximum transparency with no “tricks.” While recognizing the importance of research, they want the right to learn as much as possible and to say yes or no. Dr. Nelson talked about the differences between what parents need and want and what is required by the IRB, using a cooling study after cardiac arrest as an example. Cooling needed to begin within a half hour of arrest, so a waiver was needed. However, cooling took several hours to accomplish during which time researchers talked extensively to parents allowing them to understand the trial and then withdraw if they so chose.

Dr. Baren said that research needs to be done on the research process. It is time to recognize the need for a situationally appropriate consent that begins with presenting important concepts that allow understanding. It underscores that an informed consent is a dynamic process. Dr. Wilfond said his IRB approves short forms and brochures after agreeing to waive consent. Ms. Knudson said that even after a lengthy informed consent process, many parents do not recall any of the information. Dr. Kipnis concurred, and he described situational vulnerability that requires safeguards and ongoing education.

Dr. Fost said that he believed that subjects’ perceptions that they are being used as “a means to an end” is due to years of press about abusive research such as Tuskegee. In fact, he believes that people in clinical trials get better care than do those who receive innovative therapies. Dr. Morris agreed that lay consumers have dense misconceptions about research. Two approaches she suggested to overcome the misconceptions were:

- Community education about research
- Validation of parents’ perceptions.

Dr. Szeffler suggested that institutions begin the education by letting people know that they are a research institution that helps advance patient care. Dr. Fost said for the exception rule to be accepted, a tremendous amount of education needs to occur with IRBs, sponsors, and the general public. He proposed that an appropriate role for the NIH would be to create public service announcements, aired on a daily basis, that explain the benefits of research.

Dr. Nelson summarized discussion on this topic:

- Feasibility of getting consent versus feasibility of doing a trial
- Blended approach to consent (get consent when able and use emergency exception for others that cannot be consented)

- Balancing individual characteristics with institutional/contextual characteristics
- Consent versus communication.

Consent is an individually based event. Mr. Glantz said that general rules and procedures are necessary to cover a variety of situations. It is important to keep in mind individual rights, not group rights.

Dr. Baren offered relevant concepts to consider and study:

- Train people to properly obtain consents
- Monitor the consent process.

Dr. Lantos suggested evaluating, within studies, whether different approaches to consent have different implications. For instance, one could have half of the institutions use emergency exceptions and the other half try to get consent and then study the process, including:

- How well it works
- How much it costs
- How the subjects perceive and feel about it.

Dr. Nelson said that the Secretary of Health and Human Services can waive all of the requirements of Subparts A, B, C, and D. If these types of studies were high priority, from a regulatory perspective, they could be done.

Dr. Kipnis said that there are situations in which obtaining a signature on a form would not qualify as an effective consent. Despite this, there is a danger in assuming that it does not need to be obtained. An independent value of transparency requires diligent effort to inform even if the consent is not effective. Independent purposes are clarity, candidness, and openness.

The issue of opting out was raised. If an IRB independently decided that a study had no inherent risk or was risk reducing (minimal risk), Dr. Tyson said that opting out would be a good idea because it might increase participation, which would reduce likelihood of selection bias. It is misleading to ask people to “opt in” to these types of studies because in our society people only have to sign a paper if they are accepting increased risk or responsibility.

Mr. Glantz said that studies of informed consent evaluate what the subjects recall or what the investigators communicate. He added that studies do not show “universal uselessness” of consent; 20 to 30 percent of subjects can recall specifics of the research. The consent process, therefore, allows people who want the information and can use the information to get it.

Brandy E. Fureman, Ph.D., National Institute of Neurological Disorders and Stroke, NIH, DHHS, returned to the question of the feasibility of the trial itself. If a trial that costs \$10 million adds on a requirement for prospective consent that increases the cost to \$50 million, the study might not be done. It is not a question of weighing autonomy of the individual versus the cost. Rather, it is a question of weighing autonomy versus doing the research at all. Mr. Glantz said it is a question of how much a society values the protection of the rights of human subjects. The

argument would be that the value of the scientific information (and 90 percent does not result in usable therapies) is greater than protection of the rights of subjects.

The concept of incremental loss of autonomy was raised by Dr. Chamberlain. A patient in an emergency situation has lost autonomy so it is up to clinicians to decide what the best care is. He said that Dr. Fost has strongly argued on the superior benefits of being in a controlled clinical trial. Dr. Chamberlain added that he thinks it is unethical not to do the research and to leave patients subject to the whims of individual doctors who may provide treatments with no science to support them.

Dr. Nelson hypothesized that the research population advocated best for itself. He suggested asking members of one group (the population that might benefit from the research) if they want to wait five times longer to get the results that are important to their health. Then ask four other groups how they feel about having no research done. He thinks that if the question were put to all five groups, they would say “Waive our consent.”

Mr. Glantz agreed that scientific progress is important, but he asked if it is more important than the protection of human rights. Emergency situations are extraordinary circumstances and that is why special exceptions need to be used with care. He believes that it is also valuable to look at the impact on the investigators as well as the subjects. It is important for investigators to know that they have to engage with subjects in these ways and that they cannot “use” them to obtain data. The research community has to keep in mind that they are asking for something. Obtaining consent humanizes the relationship between investigator and subject.

Day 2

Dr. Nelson began by summarizing the highlights of the previous day’s discussion. The group had focused on two themes of patient eligibility: life threatening and unproven or unsatisfactory. A narrow interpretation of life threatening did not capture all of the elements that could be ethically justified for the use of the emergency exception to consent. Severe neurological compromise and limb loss were two situations that could be included in a broader interpretation of the term life threatening. In addition, aspects of the preamble and guidance to the rule suggest a broader interpretation of life threatening, but the rule itself could be read more narrowly.

Proven or unproven does not equate to FDA approval, and an FDA label does not preclude determining that an agent is unsatisfactory. Aspects that need to be considered when deciding if a treatment is unsatisfactory include:

- Details of the condition one is attempting to treat
- Toxicity and safety profile of the agent.

Dr. Nelson explained that an agent that is proven in the context of an FDA label could be considered unsatisfactory in comparison to other interventions that may be more effective or have a better safety profile. His interpretation of the discussion was that there is more flexibility in what the term unsatisfactory means than there is with the term unproven. As an example, even though diazepam is proven, it could be considered unsatisfactory based on the side effect of

apnea. According to Dr. Nelson, this would place the burden on those offering an alternative therapy to prove that it would not produce that particular toxicity, rather than just a head-to-head comparison of efficacy.

The discussion about the prospect of direct benefit was brief because the balancing of risk and benefit was not different in the context of using the exception. Feasibility of informed consent involved:

- Whether a trial is feasible based on a blend of eligible subjects from whom one could get consent versus those from whom one could not get consent
- Design
- Time
- Sample size.

The issue of introducing bias into the sample was raised. This might not affect the ability to prove something on a randomized basis, but it might reduce the difference one is looking for, which could extend the length of the trial and increase the needed sample size, negatively impacting the feasibility of the study. Dr. Nelson then discussed the idea of whether consent is feasible for a particular subject population, and he noted that this is the feasibility that is referred to in the regulations. Dr. Nelson pointed out that a specific timeframe in which consent could be obtained had not been determined by the group, but he acknowledged that it might be protocol specific.

The next topic concerned interpretation of minimal risk. Studies with active control comparators could be viewed as minimal risk based on incremental risk. However, no examples were raised that provided confidence that the standard could be met. This approach might not be successful with most IRBs and might only apply to narrow or limited group studies. A caveat is that incremental risk is not covered by the FDA regulations. Even if one had a waiver under the minimal risk category and community consultation was not required, it ought to take place to both respect subjects and to address their concerns about risk. Also, communication is not simply for the benefit of the subject, but there is also a salutary and morally enhancing effect on the investigator.

Mr. Glantz said that unproven or unsatisfactory is related to the life threatening condition; the regulations would have to explicitly include other conditions. Dr. Tyson discussed how excluding the highest risk patients due to inability to obtain consent could change the conclusions reached by the investigators. Dr. Nelson said that absent a blended approach, restricting a trial to only those who can give consent can seriously affect:

- Validity of conclusions
- Feasibility
- Generalizability.

Dr. Lantos remarked that another important issue that had been discussed was the degree to which the consent process truly respects the autonomy, needs, and values of the people being recruited for the study. Dr. Kuppermann added that ethics based on autonomy needs to be

balanced with not making studies so onerous that the research cannot be done. This brought up the ethical responsibility to the larger population versus the individual subject.

Discussion of Issue #4: Community Consultation

How should we implement the requirements for “community consultation” and “public disclosure”?

Dr. Nelson began the discussion on community consultation by asking:

- Who should be talked to?
- How should they be talked to?
- What will be accomplished?
- How will it affect decision making about research?

Dr. Wilfond said two points to address are:

- What is the role of community consultation (added value)?
- Research has a wide range of safeguards in addition to community consultation. So, if dissent was raised in the community, it does not necessarily mean the research should not be done.

Ms. Knudson’s institution received a waiver for consent 1 year prior to the FDA rule to study hypothermia on closed head injury. One requirement was to obtain community consultation and perform public disclosure. The researchers looked through trauma registries to learn the profile of people who arrived in emergency rooms with closed head injuries. They found the typical patient was a 25-year-old male who had used alcohol. They decided to consult parents in Harris County about the research, and the IRB determined that this should be done at 16 meetings by an investigator and an IRB member. They gave presentations at churches (English and Spanish speaking), parent teacher associations, Mothers Against Drunk Drivers, hospital volunteer meetings, service clubs such as Lions and Kiwanis, and on the radio. They asked three questions at the end of each presentation:

- Did you understand the presentation?
- Did you understand that this research would be done without your individual consent?
- Would you want yourself or a family member to participate in this research?

The researchers usually had between 85 to 87 percent positive responses, and the IRB subsequently approved the study. They have since returned to the same groups to provide updates on the progress of the study, which was very much appreciated.

Dr. Kipnis participated in a community consultation workshop a few years ago. The consensus that emerged is that it is not a vote for proxy consent for individual patients. One value of community consultation is transparency. The radio, TV, and newspaper articles reinforce to the public that researchers are not hiding anything. Dr. Kipnis is not interested so much in whether or not people think the study is a good idea as in the reasons why they do or do not think it is a good idea. The second value is “glitch detection.” Any study runs the risk of coming into conflict with one or more social values. It is far better to identify any problems before the study begins. The idea of the second value is to explore with focus groups whether there are any strong

objections from the geographical community or the community of potential subjects. Researchers also must be prepared to alter the study based on findings from the focus groups. Otherwise, the consultation is a fraud. Dr. Szeffler added that investigators can learn a lot about the feasibility of the study and potential problems from community consultation.

Dr. Fost presented a conceptual framework for discussing community consultation adapted from NIH-funded work by Pilar Ossorio, J.D., Ph.D., and Dan Hausman, Ph.D., University of Wisconsin.

What to call it?

- Community consultation
- Engagement
- Dialogue.

What are the goals or reasons for it?

- Individual consent inadequate
- Understand cultural issues
- Improve trust with investigator and institution
- Obtain ideas to improve study
- Enhance recruitment.

Definition of community:

- Geographic
 - Neighborhood
 - Municipality
 - County
 - State
 - Country (recall “benefits of research” debate)
- Political
 - Representative groups (for example, city council)
 - Representative leaders (elected or appointed).

Methods:

- Advisory group
- Surveys
- Town meetings
- Focus groups.

Reasons not to do it:

- Group pressure for individuals to enroll
- Mobilize opposition; empower opponents
- No such thing as “community”
- Limits on freedom of inquiry; investigators, sponsors
- Can deter or reduce research on emergency conditions
- Time/monetary costs

- Fear of adverse publicity.

Dr. Fost was a member of the data monitoring committee (DMC) for the Baxter cross linked hemoglobin project, which he thinks is the first study done under the new rule. The DMC reviewed and approved the community consultation methodologies for 14 of the 16 participating sites. The company had not provided written guides for this process.

Dr. Fleischman said that there is a 15-year database of community-based participatory research. The Centers for Disease Control and Prevention (CDC) Urban Health Centers have been doing community engagement for years. The IOM Fall 2005 report “Ethical Issues in Housing Health Hazards Research for Children” lays out the literature on community engagement in research. It does not specifically address emergency exception, but it does cover all of the issues raised in Dr. Fost’s presentation and encourages aggressive and respectful engagement with communities. It argues that consultation is not informing and is not simply glitch detection. Consultation allows communities and institutions to establish a collegial relationship and share the view that research is good. He agreed that communities ought not to be allowed to stop important research. However, when communities question priorities, it is smart for the institution to listen. He suggested that participants each obtain and read a copy of the report and said that he would ask the IOM if they would supply copies.

Dr. Baren said that based on the recent consensus conference in New York, investigators expressed both eagerness and concern about community collaboration. To focus on practicality, she asked Ms. Knudson to estimate the cost of the 16 meetings she held. Ms. Knudson said the cost in time for the IRB, speakers, nurses, and participants was enormous. Dr. Baren asked whether they published the results of the collaboration with the community, and Ms. Knudson said the results were not published other than an article in the local newspaper. In addition, they sent quarterly reports to OPRR. Dr. Baren described a more spartan model of community consultation in 1996 using phenytoin in the study of posttraumatic seizures in severely head injured children. The researchers interviewed a proxy population of parents of children with minor head injuries at three emergency rooms. The vast majority of parents said they would be willing to forego consent in order for their children to participate in the study. Investigators were frustrated because the regulations were vague, but Dr. Baren said that she valued the vagueness because community consultation is not one size fits all.

Dr. Lantos said that there is a well organized structure of community leaders (church pastors) in the south side of Chicago. If a study is endorsed by community leaders, church members will sign up. However, the pastors want something in return (for example, a clinic for the uninsured in the neighborhood). A philosophic issue that he raised concerned the people who do not want to participate in the study. He asked whether the study should be cancelled if a certain number of people in the community were opposed (for example, 10 percent). He believes that if a majority of a community is opposed, the study should be cancelled. He asked what participants thought should happen if there were a vocal minority in opposition.

Dr. Fleischman described a program in East Harlem in which an ongoing dialogue occurs. He described an enduring, meaningful partnership between an institution and its community.

Investigators do not meet only when they want to discuss a specific study. Instead, they teach community members to write grants and have helped with sanitation problems. So, discussing a new research study is simply an agenda item for regularly held meetings. He added that community engagement is not about obtaining community consent. He does not know the number of people in the community who approve or disapprove of research, and knowing is not necessary.

If a study compares two standard therapies or is very low risk, Dr. Fost said that it does not matter how many community members approve or disapprove. If people are given ways to opt out, it also does not matter how many people approve or disapprove. Dr. Fost also pointed out that obtaining consents in the traditional way still only results in 20 to 30 percent of people who give a truly informed consent. It really only provides legal protection to the institution. He said, after questioning, that if there were major community opposition, he would recommend not doing the study, but for political, not moral, reasons.

Dr. Kuppermann described the community consultation process in PECARN. The contract with DHHS required community consultation about a research agenda, not a specific trial. The people they consulted included:

- Local members of national organizations
- School teachers
- Leaders in the minority populations (African American, Southeast Asian)
- Political staffers.

After describing the general research agenda, there was an interactive session followed by subsequent meetings every 3 to 6 months. The discussions resulted in only minor changes of the agenda, but there was a respectful exchange of ideas.

Dr. Nelson summarized the discussion on this topic as:

- The community is study specific.
- The results of the consultation depend on the nature of the study.
- Values include transparency, glitch detection, respect, and engagement.
- Nesting community consultation into a broader, ongoing community engagement is important.

Dr. Schalick said that there is a lack of respect in many communities for research. Education is part of the value of transparency, but it has a different flavor. Educating communities about the value of general and specific research efforts is very important.

Community consultation is required by the regulations for emergency research without consent. Mr. Glantz pointed out that community consultation does not:

- Make an unethical study ethical
- Determine ethics by consensus
- Provide an endorsement.

Community consultation is not a substitute for consent. The regulations say that its purpose is to provide additional protections to the rights and welfare of subjects. It is primarily a political undertaking and the primary benefit is transparency. The percentage of support in the community (90/10 or 10/90) is not an important question, as it has nothing to do with whether an IRB will approve a proposal. He is not sure why community consultation is specifically required for only this type of research. One of the weaknesses of community consultation is that it is done by the institution; Mr. Glantz wondered if this shows that having community representation on IRBs is a failure. He added that this exceptional case might not be necessary if community representation on IRBs was greater.

Dr. Prentice said he was invited to join an advisory committee to set up three conferences in the Dakotas designed to:

- Train researchers to do research in Native American communities
- Train Native Americans to set up their own IRBs
- Train Native Americans to be IRB members.

At these three conferences, community consultation was discussed a great deal. Dr. Prentice agreed with Dr. Fleischman that community consultation is a sign of respect. To do research in Native American communities, researchers may need to get permission from three IRBs: the research institution's IRB, the Indian Health Service IRB, and the tribe's IRB. Researchers also have to get the approval of the tribal council, which gives proxy consent for the community. In addition, an ongoing community consultation process is required. The communities also want the ability to modify the protocol and to get ongoing results as the research is done. Often, tribal permission is necessary prior to publishing results of research. Dr. Prentice asked: If one ethnic group in a varied community was very opposed to the study, would researchers need to exclude that group from the study?

Mr. Glantz said members of a focus group do not represent the wishes of an entire community and therefore no one can be excluded based on focus group opinions. It is called community consultation, not community consent. Dr. Lantos said that in the case of waiving consent, the community holds more power because individuals are not able to give individual consent. Dr. Fost said that in many cases people in authority stop people from participating in research. Examples are IRBs, the Secretary of DHHS (407 process), and tribal councils. Dr. Kipnis views community consultation as a three-step process:

- Meetings and discussion
- Proposal modification if it rides roughshod over community norms
- Disclosure (report to the community prior to the study starting).

Mr. Glantz commented that much of the discussion had not focused on the emergency nature of these studies. He said that the issue of a community's ability to change or veto research is a separate discussion. The most pertinent issue is why does only the emergency exception require community consultation and what is the meaning of community approval or disapproval. Dr. Fost said he was part of the coalition that wrote the template that eventually became the FDA rule. At the time, the discussion included how community consultation would be a good idea for all research and acknowledged that the single public member of IRBs was not always effective at

representing what the community thought. The reasons for requiring it for this type of highly charged research were:

- Patients in these setting frequently die.
- The research is often done in inner cities.
- It involves a deep taboo against doing research without informed consent.

Dr. Morris said that most of the discussion concerned using community consultation to assess or gain endorsement of a study. While important, another aspect to consider is community consultation as a way to gather important information, especially from people in the population affected (for example, parents of children who have cardiac or respiratory arrest). This would be a real contribution, rather than just changing “the margins” of the protocol.

Dr. Fost said that the Baxter experience was interesting in terms of changing the protocol:

- A minority person should have been on the DMC.
- The idea of opting out had not been raised until after the community consultation.
- They learned how different centers did community consultation.

He added that communities do not have veto power, just as the community member of the IRB does not. However, good suggestions may lead to change. Dr. Baren clarified that community consultation is to inform IRBs, not investigators.

Dr. Nelson began the discussion about public disclosure, which is required before an emergency exception study starts and after it is over. Dr. Fleischman noted that disclosing findings can result in unintended negative consequences. He suggested first talking with community leaders to obtain helpful feedback on how to disclose findings. Dr. Szeffler noted that disclosure needs to be done carefully so that confidentiality of subjects is not compromised.

Dr. Nelson reminded participants that he would write a summary of this meeting that would appear in the *American Journal of Bioethics*. He offered to send the draft electronically to meeting participants for comments and said that he hoped a public meeting might be held after the FDA guidance is released. In answer to a question from a participant, he said that the FDA attorney advised FDA employees not to attend this meeting in order to prevent the appearance of conflict. Dr. Giacoia added that the reason was to prevent any suggestion that this meeting might influence the development of the new guidance. Julie Kaneshiro, M.A., Office of the Secretary, DHHS, was asked if the Office of Human Research Protections (OHRP) expected to review and comment on the draft guidance, and she said that the FDA had said that would occur prior to release.

Mr. Glantz said it would be worthwhile to discuss why the exception rule has a special impact on the pediatric population. Dr. Fleischman said that adult subjects in emergency research are often incompetent and unaccompanied, but children usually have a parent present. Whether informed consent can be obtained is often an issue. Mr. Glantz said that parents of severely ill or dying children are often not able to be rational or dispassionate; however, if a parent is physically present, he does not think these rules apply. Dr. Fleischman disagreed, which led to a discussion of the difference between the terms “unavailable” and “not feasible.” Dr. Prentice said that the

parents' mental state and the therapeutic window both affect ability to obtain an informed consent, but he felt that granting an exception to informed consent if parents were present was stepping onto dangerous ground.

Dr. Morris said that if a parent is present, communication is required, but if there is no way to meet the legal definition of informed consent, then the exception can be used, assuming it is not minimal risk. The regulations require that consent be obtained when able. Even if a valid consent is not obtained, a valid opt-out is possible. Dr. Kipnis said that protocols that use the emergency exception should be required to include parameters for communication so that parents get as much information as possible given the circumstances even if consent is not possible. Mr. Glantz said that to enroll a child without consent if a parent is present is very troubling. Dr. Nelson and others discussed the difference between clinical informed consent and research informed consent (as defined by IRB regulations). Barriers to obtaining informed consent for emergency research are:

- Institutional requirements to read the Health Insurance Portability and Accountability Act form
- Institutional requirements to read the consent long form
- Short form (45 CFR 46.116) is rarely used
- Difficulty of getting short form approved by IRBs
- Emotional state of parents
- Distressing for investigators to obtain permission in a short therapeutic window.

Dr. Tyson said that requirements for emergency exceptions should be no more demanding than those for innovative therapies or the existing double standard will worsen. He described a neonatal hypothermia trial for asphyxiated neonates in which there was a therapeutic window of 6 hours. He found the consent process that required waking up a new mother who had just had a caesarian section to be cruel. He has asked his institution to consider requiring clinicians who want to give innovative therapies to develop a consent form. Mr. Glantz said that the ethical and moral power of consents do not come from the documentations and forms. He views each of the following situations to be ethically distinct:

- Parents are not present.
- Parents are present but there is no time for communication.
- Parents are present and a therapeutic window for discussion exists.

Dr. Chamberlain suggested adding parents who are not emotionally receptive to the list. The group then discussed the moral purpose of the conversation versus the ritualistic completion of the form. Dr. Kuppermann said the role of the short form is unique due to both the short therapeutic window and the state of the parents. He described a study in which the short form was used by half of the 20 sites in PECARN for a bronchiolitis study (the window was 2 hours and the parents were usually not too distraught). The investigators will compare the success rates at both groups of sites.

Dr. Nelson summarized the discussion by saying the situation is complex when the legally authorized agent is the parent who is present. Communication between the parent and investigator is complex and important. Dr. Lantos said that the discussion points out the

importance of studying the informed consent process. Another unique situation is that sometimes the parent is herself a patient (pregnant woman). Dr. Finer said that the exception should only apply to the original intervention, and then consent is required for the ongoing process of the study (additional imaging, data collection, questionnaires, and others). Dr. Tyson also said that using the exception in pediatric research has higher stakes in terms of life years, burden to the family, quality of life, and societal costs.

The data on maternal decision making are sparse. One way to generate this information is to piggyback studies of the informed consent process onto existing trials. The closer this occurs to the event, the more accurate the data may be because the outcome does not affect mothers' perceptions. Dr. Nelson asked whether research on informed consent might increase the chance of people pulling out of the study. Dr. Chamberlain said that if it occurred it would show that the informed consent process was flawed, and the IRB should want to know that. Although Dr. Kuppermann supports studying the informed consent process in principle, in reality it means that the family is subjected to another long process after completing the long form for the initial consent.

Dr. Finer made a few additional points:

- People who do consent might change their minds if they are asked to enroll in a study on the informed consent process.
- Families that opted out might reconsider in the same situation, so it could work both ways.
- Just because parents change their minds does not mean they went through a flawed process.
- Studies of informed consent might help institutions learn the costs (time and money) of the informed consent process.

Discussion of Issue #5: Institutional Review Boards

What are the strengths and weaknesses, opportunities and threats, presented by the existing system of IRB oversight for pediatric research using the emergency exemption from informed consent (EFIC)?

Dr. Kipnis opened the discussion by saying that the importance of transparency had been stressed throughout the meeting. He said that many protocols arrive at IRBs with confidentiality agreements, and members of the IRB and investigators are barred from even reading the protocol until they sign the agreement. This results in public members of the IRB being denied access to the protocol, which creates a conflict between proprietary and ethical issues. His belief is that the requirement for transparency trumps the company's proprietary interests. He does not believe that IRBs should approve protocols using the EFIC if the protocols are protected by confidentiality agreements. Dr. Kipnis said he wrote to a chief executive officer to obtain a consent form for a protocol protected by such an agreement, and he was denied access.

Participants discussed how a consent form that is intended for the public could be construed as being confidential. Dr. Nelson added that the FDA guidance suggests that the consent form could be part of the public disclosure. He also said that IRB chairs have posted the title of protocols on the IRB Forum, which is also open to sponsors and the public, to ask if other chairs had seen it

yet. In two instances, sponsors have contacted institutions accusing them of publishing confidential information. This results in less communication among IRBs. For EFIC studies, information goes from the IRB to the sponsor without passing through the investigator. If the IRB does not approve, the sponsor is notified and must then inform the other IRBs. However, the regulations do not say what happens if the IRB does not make a final determination. There have been instances in which IRBs had ethical concerns about specific trials, but their views were never reported to the sponsors because the IRB never disapproved the studies. In these cases, other IRBs do not learn about the ethical concerns. Dr. Nelson added that the regulations do not require IRB to IRB communication, and IRBs that communicate about trials with confidentiality agreements risk legal action.

Mr. Glantz said that subjects know what is in the consent form and they can talk to whomever they wish about it. In his view, disclosure means that if a company wishes to waive informed consent procedures, it waives the right to secrecy about the trial. Full disclosure cannot be based on what the sponsor chooses to disclose. To be eligible to apply to use EFIC, full disclosure must occur of everything related to the research, including the entire protocol and consent form.

One participant said that at his institution, a potential subject who asked for a copy of the full protocol was put on the study “do not enroll” list. Ms. Knudson said that no one had ever asked her IRB for a copy of the entire protocol, and Mr. Glantz replied that people do not know they exist. If protocols were put on a Web site, they would be available for subjects who wish to read them. Dr. Tyson said there should also be a commitment to publish or make available on the Web site all study results, including negative results. Participants then discussed the language in the regulations concerning release of study results. They also discussed the new requirement of the major journals that results of clinical trials will only be published if the protocol is registered. Several participants described how companies were changing names of clinical trials and using other maneuvers that have resulted in the requirement not working as intended.

Dr. Kuppermann described how PECARN is trying to facilitate communication and education among IRBs because half of them have never seen or approved an EFIC study. It was said that an informal network of IRB chairs and administrators exists and that much discussion of protocols occurs in that way. An investigator asked if she was prohibited from sharing IRB comments about a protocol with investigators at other institutions, which frequently happens during network conference calls. The general response was “no” but she was encouraged to seek the advice of her institution’s attorney. Dr. Zimmerman described a newsletter for the 100-site ZIGRAS trial that contained common IRB roadblocks and ways used to overcome them.

Dr. Prentice brought up the issue of independent IRBs and their role in EFIC studies. Dr. Fost said that it was not a good idea to use a distant (whether commercial or not) IRB for exception studies because of the local community issues. He thinks that IRBs at each individual institution should be required to review studies and that community hospitals that do not have an IRB should be excluded from this type of research. Dr. Nelson described a model in which the lead institution would perform a robust community consultation that would inform all subsequent sites.

Dr. Kipnis said that Special Protocol Assessment (SPA) is a special status issued by the FDA that binds the FDA and the sponsor to a specific, finished protocol. He thinks this runs counter to doing community consultation because it prohibits the investigator and sponsor from making changes in the protocol. Just as confidentiality agreements interfere with transparency, the SPAs compromise community consultation. He suggested that EFICs not be approved for SPAs that prevent sponsors from making appropriate adjustments to the protocol. Dr. Nelson confirmed that any requested changes based on ethical issues are precluded from being made to protocols with a SPA.

Dr. Kipnis said the issue is bigger than just community consultation because IRBs cannot change SPA protocols either, and they are not informed when they are sent a protocol that it is covered by SPA. He said it is a system that misleads IRBs and the community. Dr. Lantos described some of the background, including the FDA Modernization Act of 1998, which created the SPA status to streamline approval processes. The SPA is issued before the protocol goes out for IRB review. Dr. Wilfond asked if it has to occur that way, or if it could be issued after community consultation. It was pointed out that IRBs usually do not change the science in protocols. Instead, they tend to add restrictions to protocols. Dr. Nelson said that articles about this issue will soon appear in the journals *IRB* and *Journal of Bioethics*.

Dr. Nelson said that if he wanted to share his IRB's insight and advice, he would not do it without the investigator's consent. If the networks provided information to permit local IRBs to share information, it would help create a "best practices" approach rather than a "most restrictive, legal interpretation of regulations" approach. Dr. Szeffler said that could help prevent delays in recruitment. Dr. Kuppermann described the anxiety this can cause with investigators. PECARN was planning a minimal risk, observational study, and 23 of 25 sites approved the protocol. One of the sites that did not approve the protocol wanted to contact all of the others to share their conservative interpretation. Guidelines for fair IRB communications would be helpful.

The group then discussed whether IRB chairs had an ethical obligation to contact other IRB chairs if they feel something is ethically wrong with a study. Dr. Nelson said that most often it was an issue of legitimate differences of opinion on how to interpret the regulations. Other participants made the following points:

- If such contact occurs it will most likely be over the emergency exception due to ethical concerns.
- Two participants said their IRBs had written letters asking why other IRBs approved a study but neither got a response.
- Sharing thoughts on the IRB Forum has prompted some IRBs to re-review approval of studies.
- OHRP could be contacted if an IRB member is concerned about a potentially unethical trial.
- OHRP is mandated to review a study if one site of a multicenter study refers it for a 407 review (45 CFR 46.407), and OHRP now has the authority to halt the study. What typically happens is that OHRP notifies the funding agency (usually the NIH) of the review, and the funding agency voluntarily suspends enrollment pending the secretary's determination.

- OHRP should not be contacted other than for advice. A letter should be written, and the IRB (and sponsor and network if appropriate) should review the concern and respond in writing.
- Community to this point has been defined as the community from which the subjects will be drawn and the community in which the research will take place. Why not extend the concept of community to include the community of IRBs (such as the upcoming National Children's Study meeting of IRB chairs)?

Dr. Lantos pointed out that most of the discussion up to this point concerned the IRB's role in protecting the investigator, institution, and the sponsor, but not the subjects. He felt that until these various IRB roles are discussed separately, no progress can be made in identifying ethical conflicts. He said that in the context of an emergency exception for informed consent, confidentiality agreements should be waived.

Dr. Kuppermann said that PECARN had discussed setting up a centralized IRB but decided the network was not large enough. Members then discussed setting up a committee to discuss such issues. Ms. Knudson thought this was an excellent idea that would allow a process for bringing concerns back to individual IRBs. Dr. Sullivan agreed as well. She also suggested considering inviting experts for more input, especially for IRBs first considering emergency exceptions for children.

Dr. Kipnis asked how often and under what circumstances the reasons for IRB disapprovals are shared with other IRBs. Dr. Szeffler said the notification usually occurs when there is a major modification in the protocol resulting from the disapproval. This communication from the investigators includes the rationale for the change. Dr. Lantos said the whole IRB system was designed not to have accountability, unlike the legal system, which is designed for full disclosure. He compared it to asking a jury to publish its decision. Dr. Nelson responded that the EFIC requirements for communication are different than for any other research process. In all but EFIC research, information goes through the investigators. But for EFIC research, IRBs are required to go to the sponsors, which are required to relay those issues to the FDA and all of the other IRBs that have reviewed the protocol. Dr. Fost said that his experience with the National Cancer Institute central IRB is that it is tremendously useful for first review and continual review. It often provides insights that local IRBs do not have.

Dr. Nelson summarized the discussion on IRBs:

- The IRB oversight should be local to facilitate community consultation, but some uniformity of IRB oversight across a specific trial is desirable.
- Different mechanisms were discussed to achieve that uniformity.
- Open communication and transparency among IRBs reviewing the research are important.
- Investigators are a key part of the protocol review process.

A participant asked whether the emergency exception was ever applied to pregnant women. Dr. Tyson said that prior to the emergency exception rule, a multi-country, randomized trial of magnesium sulfate was done for women with eclampsia. Criticism arose concerning the harm done to women by delays in getting the trial completed. Dr. Prentice said that DHHS regulation subpart B provides additional protection for pregnant women and fetuses. The FDA regulations

have no additional protections other than subpart D. The DHHS waiver of informed consent under emergency circumstances has no applicability for research involving pregnant women. He said that if a study involving pregnant women is partly DHHS funded and has requested an exception from consent, or if it will be done at an institution that has agreed to comply with subpart B, the study cannot be done.

Ms. Kaneshiro said that information was correct. When the exception was drafted, two populations were excluded: pregnant women and prisoners. Dr. Prentice said this nonharmonization of FDA and DHHS requirements should be included in IRB education efforts. When questioned, Dr. Prentice said that viable neonates are not excluded, but if a neonate is of questionable viability, it falls under subpart B. Dr. Nelson said that there has been much criticism of the Bush administration's wording of subpart B, but they have made it clear that subpart D should apply. He believes that every neonate in a NICU is of uncertain viability until term, so subpart D applies and subpart B does not.

Dr. Prentice said if research is federally funded or if the institution has agreed to comply with subpart B, the waiver does not apply to pregnant women, fetuses, or neonates unless they are viable. He then read the definition of viable neonate and said that he thought subpart D only applied to those neonates that had a good chance of survival. He then read the definition of neonates of uncertain viability and the additional conditions that must be met. The most pertinent one requires the IRB to determine that the research enhances the probability of survival of the neonate (46.205.b.1 and 2). Dr. Nelson said that it is a problem and it depends on the IRB's interpretation of uncertain viability.

Discussion moved on to research ideas, including:

- The importance of funding outreach to the community and education about research and its protections. Outcome measures such as heightened awareness or increased participation would be worth evaluating.
- A comprehensive analysis of EFIC efforts that were approved, disapproved, or extensively discussed would help to clarify issues and to plan future studies. This would include collecting information on what has been done and identifying obstacles that arose at all levels, including with investigators, sponsors, DMCs, FDA, and IRBs. Confidentiality agreements might make this hard to accomplish, although it was noted that three studies have been published on the research sponsored by Baxter.
- Perform more ethical analyses of trials using the emergency exception in pediatrics.
- Use focus groups to do glitch detection to avoid offending cultures.
- Do sociological homework to determine how many people are reached by community consultation and to identify which strategies are most effective.
- For exception of consent for emergency research in children, the most important outcome is how the parents of children who were enrolled in the studies feel about what has happened to their children.
- Most of the goals mentioned so far are not measurable (for instance, how much respect was shown to community).

- One measurable factor is the percentage of eligible people who are enrolled in the study. Because of the exception from consent, for the first time one can evaluate why all eligible subjects were not enrolled.
- Another measurable factor is the time it took to complete the study compared to the time projected.
- Evaluate the impact of the community consultation on researchers.
- At the end of community consultation focus groups, ask the following questions: How was the presentation? Was it useful? Was it an effective dialogue? Did it affect your views on the research and the institution conducting it?
- Another participant said that basic information should be obtained first: How long did the community consultation take? How much did it cost? How satisfied were the investigators? How reassuring was it to parents of potential subjects?
- It was noted that many of the proposed outcome measures did not have comparison groups. A participant responded that one could compare models of community consultation at different sites participating in the same study. Another possible way to measure outcomes is to compare different approaches to informing parents that their children have been enrolled without consent (for example, compare using written materials to not using written materials).
- General awareness is not the best goal. For instance, attempting to notify a percentage of the general population about research will not result in high numbers. However, by focusing on specific populations (for example, parents of children who have seizures and are at risk for status epilepticus), community consultation may result in higher levels of awareness.
- If transparency is the primary goal, then evaluation depends on who is looking “through the glass.” One way to see if transparency is indeed in place is to have independent monitors assess how much information they could obtain to answer basic questions (for example, what research studies on children are being done in the community) and compare that to how much information is available.
- Using a window as a metaphor is quite effective because one cannot make people look through windows, but one can enable people who want to look to do so. The disclosure part includes letting people know that there is a window.

During the last half hour of the meeting, participants shared thoughts about the discussion on emergency exceptions in pediatric research and expressed appreciation for being invited to participate. Points they made included:

- The importance of talking to people (subjects) despite using an emergency exception to consent.
- Developing better ways to foster communication among IRBs.
- The value of obtaining more information and performing more research on the experience of research subjects.
- The difference between minimal risk and incremental risk and how to approach that with IRBs.
- Within networks, getting a representative from each IRB to come to a meeting to discuss any problematic or controversial protocols.

- Regulations have been written based on views of investigators, regulators, ethicists, and physicians. More information is needed from patients who received innovative therapies and from actual or potential subjects of research studies.
- It used to be deemed impossible to do research in emergency settings, and the new regulations provide an opportunity to do good research. Now that regulations are in place, a workable process to do the research needs to be developed.
- Facilitating communication can prevent possible damage from a bad event.
- A team approach to creating the best process is needed, and having representatives from various networks at the meeting might facilitate that effort.
- Much variability in people of good will exists on the topics discussed. Identifying the variability among the network IRBs will be critical to smooth over some of these issues on a pragmatic level.
- The idea that community consultation and education ought to extend beyond situations involving the emergency exception is new and important.
- Using a waiver for minimal risk can be extended to the comparison of treatment modalities that are both within the standard of practice and the absence of evidence showing the inferiority of either one. This could be a major advance in the ethics of doing emergency research.
- These interesting and enlightening deliberations will help OHRP thoughtfully evaluate the secretarial waiver in the preamble of their publication which is the equivalent of the FDA's waiver. They have committed to evaluating how the waiver is being implemented.
- This meeting will help IRBs better deliberate to help both investigators and the public.
- The emphasis should be on how extraordinary it is to do research without consent and that it is presumptively unethical. It requires justification at every level.
- At this stage, try to avoid being mired in bureaucratic and compliance issues because the underlying important issues are values and ethics.
- The group never seemed to reach clarity on how this kind of research is unique in children.
- The embedded idea that research is bad or dangerous needs to be replaced, through education and communication, with the belief that research is good and beneficial to people. This misconception arose due to unethical events that happened decades ago when research was unregulated. The American public, press, and Congress should be introduced to the concept of "research is good" through a massive educational campaign.
- The importance of communication between investigators and subjects and among research sites and IRBs.
- Balancing protection and autonomy of subjects with the importance of conducting research in emergency settings that provides benefits to individual subjects as well as society at large.
- The presumption that "research without consent is unethical" is necessary. Research has been made safe due to regulations and oversight imposed on researchers. Keeping this oversight in place, especially around research without consent, is important.
- A fundamental ethical problem is that the two major agencies that oversee research cannot agree or communicate with each other or researchers. There ought to be harmonization of the rules and they ought to be made transparent, including full disclosure to investigators.
- The current informed consent process is fundamentally flawed and further research is needed to start over and redesign a new process.

- The divergence between the legality and the morality of doing the right thing was apparent throughout the meeting. If IRBs narrowly focus on the legalities, they may totally miss the point. If the process can be led back to doing the right thing, it will be a big contribution.

The group gave Dr. Nelson a round of applause for his leadership role as a moderator. Dr. Giacoia thanked the planning committee and Dr. Nelson for organizing the meeting and allowing such a wonderful exchange. He would like to share the meeting minutes with other NIH institutes to help continue this important process. Dr. Mattison thanked Dr. Nelson, the planning committee, and each member of the panel for clarifying how many research questions need substantially more attention. His hope is that these discussions will lead to a series of helpful activities.

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